

INFLAMMATION AND WOUND HEALING

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INFLAMMATION

- Response of vascularized tissue to infection and damaged tissue that brings cells and molecules of host defense from the circulation to the sites where they are needed in order to eliminate the offending agent.
- Goals of Inflammation
 - To get rid of initial cause of cell injury.
 - To get rid of consequences of injury.
 - To prevent other organ system damage
 - Initiate the process of repair

- Inflammation

Cardinal signs of Inflammation

1. Rubor- Redness.
2. Tumor-Swelling.
3. Calor-Heat
4. Dollar-pain
5. Loss of function(funcio laesa)



- Causes of inflammation:
 - Exogenous
 - Mechanical
 - Physical
 - Chemical
 - Biological
 - Endogenous
 - Circulatory disorder,
 - hypoxia
 - Endogenous protease release
 - Immunocomplex formation

INFLAMMATION

CAUSES OF INFLAMMATION

1. Infection-
bacterial, viral, fungal, parasitic, microbial
toxic
2. Tissue Necrosis
3. Foreign Body-dirt, splinters, sutures
4. Immune Reaction



Steps of Inflammation

5R's

1. **R**ecognition of injurious agent
2. **R**ecruitment of leukocytes
3. **R**emoval of agent
4. **R**egulation of the response
5. **R**esolution

TYPES OF INFLAMMATION

- 1.ACUTE INFLMMATION
- 2.CHRONIC INFLAMMATION

Stimuli

can be triggered by a variety of stimuli

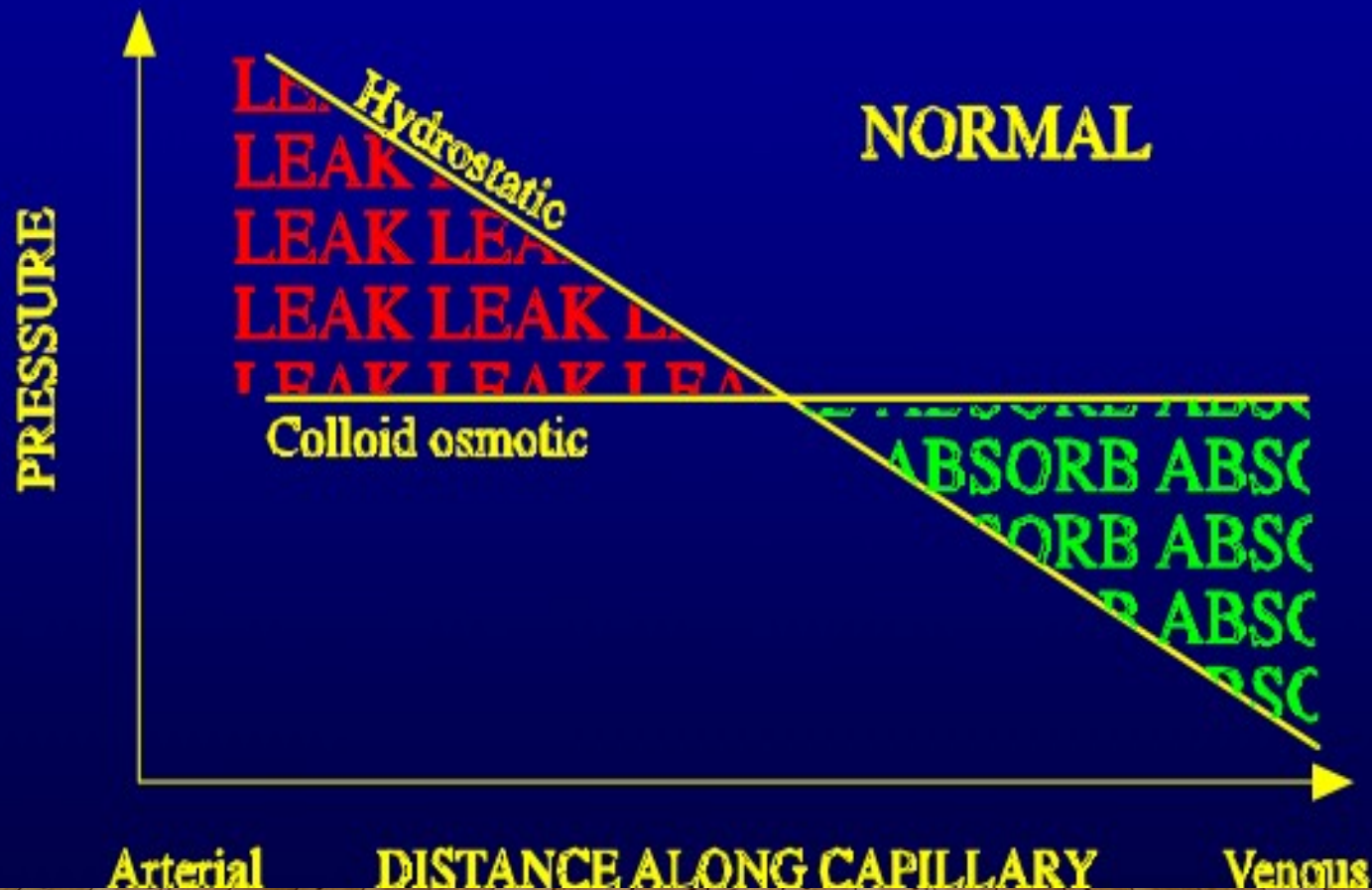
- Infections
- Trauma
- Physical & chemical agents
- Foreign bodies
- Immune reactions

ACUTE INFLAMMATION

- Rapid onset
- Short duration
- Subsides when goals are fulfilled

'Starling's law'

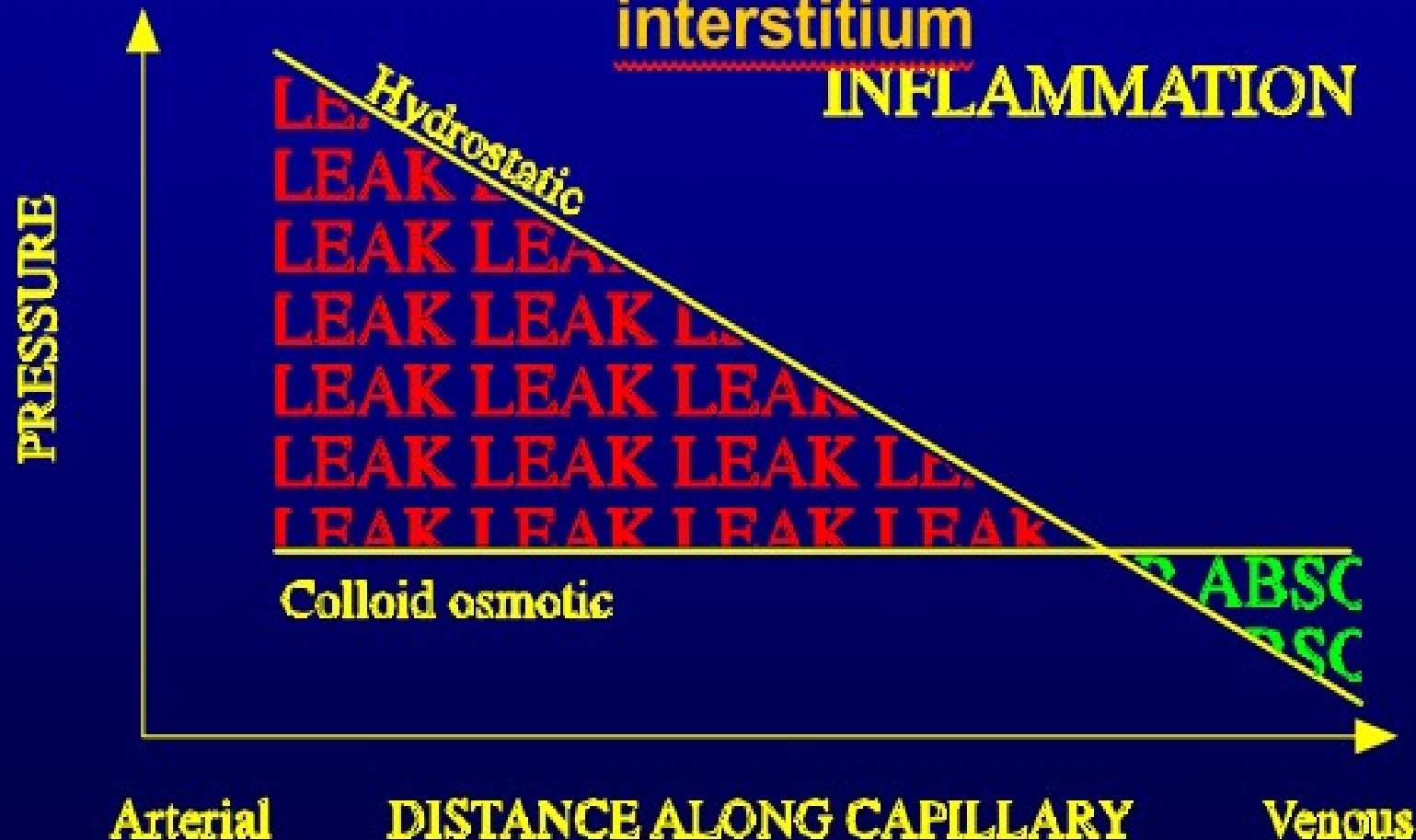
relating to fluid flux between vessels and
interstitium



'Starling's law'

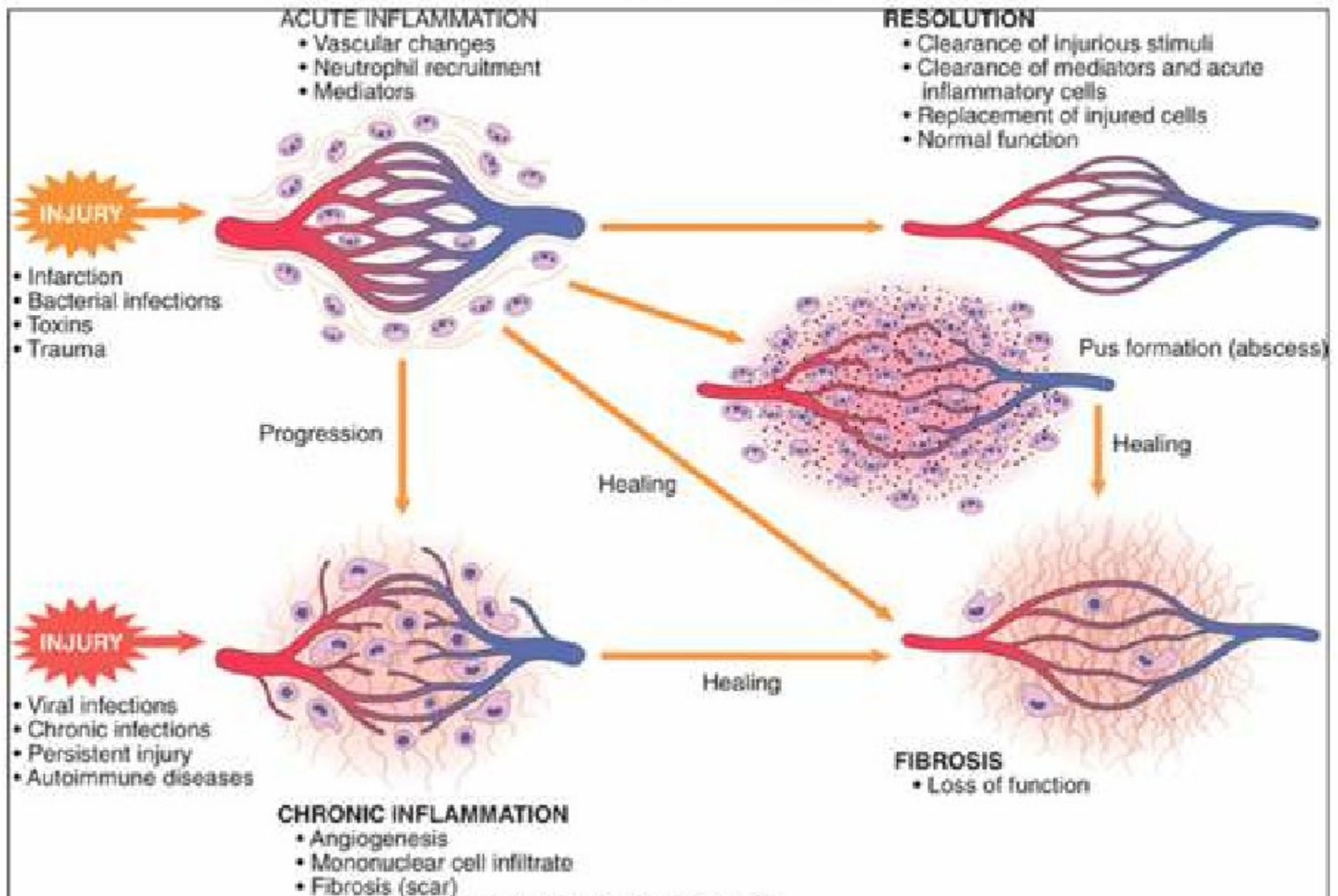
relating to fluid flux between vessels and
interstitium

INFLAMMATION



Outcomes of Acute Inflammation

Resolution, healing by scarring (fibrosis), or chronic inflammation



OUTCOMES OF ACUTE INFLAMMATION

Typically have three outcome :

1. Complete resolution
2. Healing by connective tissue replacement
3. Progression to chronic inflammation

FEATURES OF ACUTE AND CHRONIC INFLAMMATION

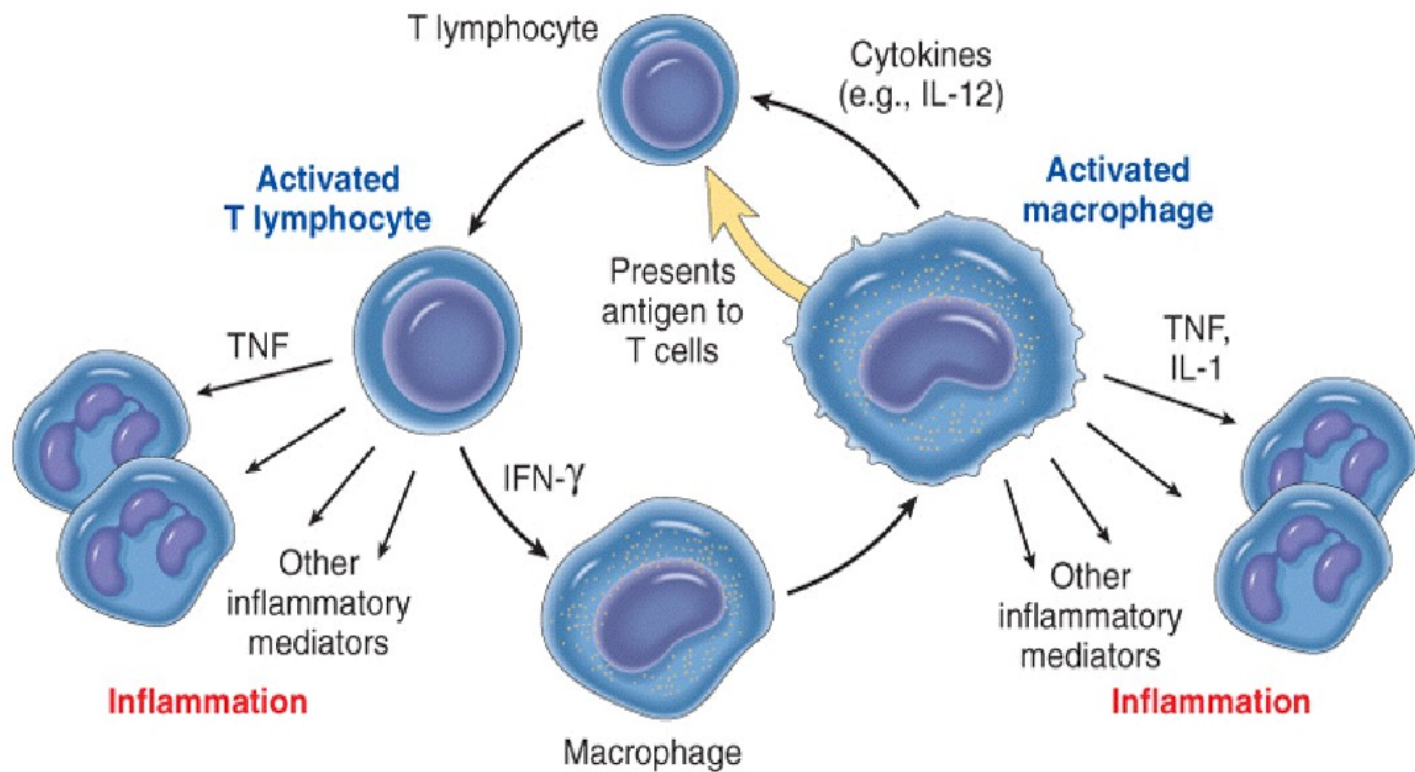
FEATURES

ACUTE

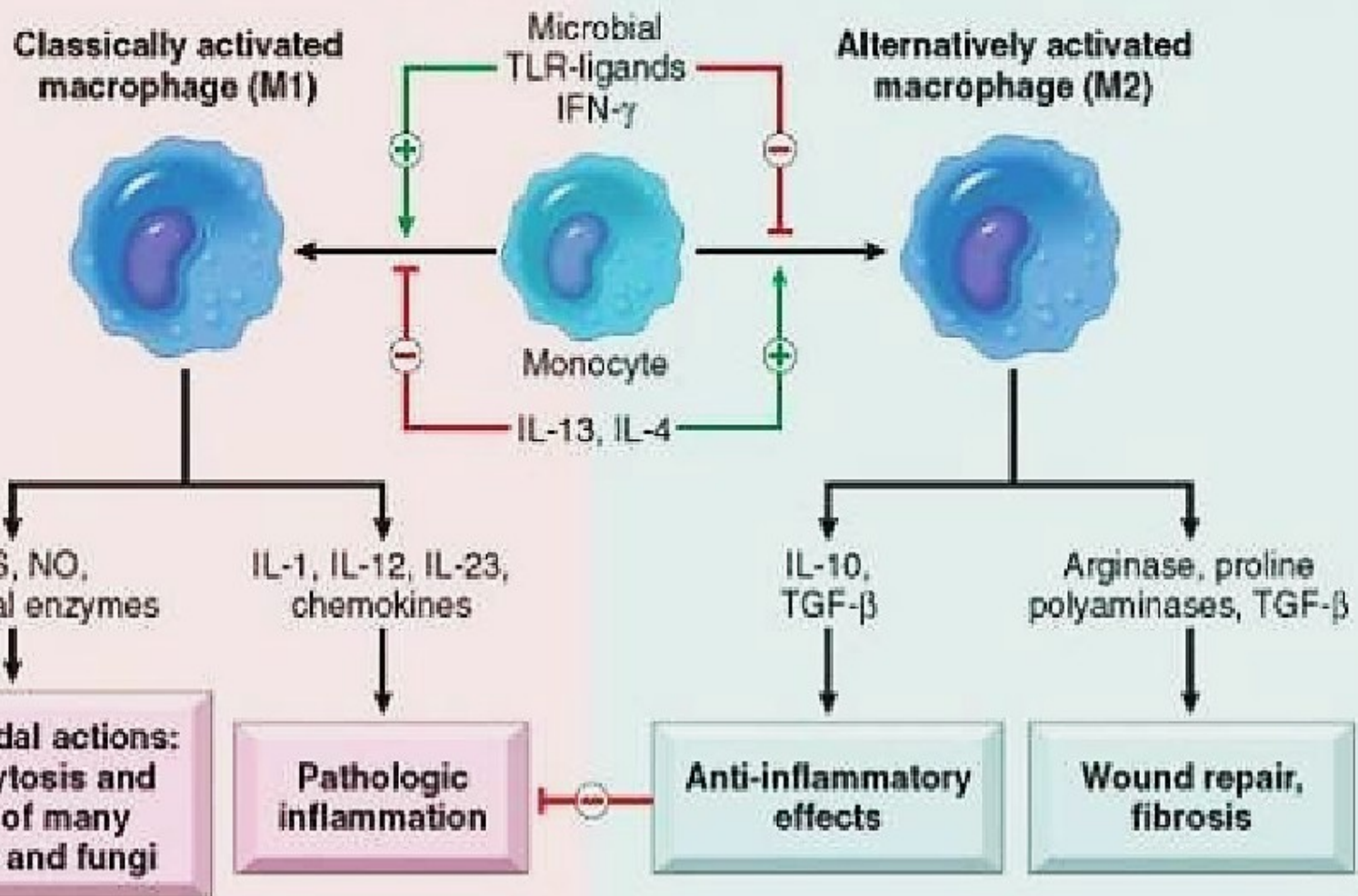
CHRONIC

■ Onset	■ Fast:min to hrs	■ slow: days
■ Cellular infiltrate	■ Neutrophils	■ Monocytes macrophages and lymphocytes
■ Tissue injury	■ Mild self limited	■ Sever and progressive
■ Local and systemic signs	■ prominent	■ Less prominent

THE CELLS



INFLAMMATION: REGULATION



Microscopic changes

Original observations made with frog foot-web and rat mesentery.

- Dilatation of vessels
- Sludging of RBCs
- Fluid leaks into interstitium
- Implies increased permeability of vessels: (not to water but to protein).
- Cells move into interstitium

Definitions

- A **TRANSUDATE** has a low protein content, usually caused by alterations in hydrostatic or oncotic pressure.

Implies a hydrostatic (pressure) problem.

- An **EXUDATE** has a high protein content, caused by increased vascular permeability.

Implies an inflammatory process.

MAJOR COMPONENTS OF ACUTE INFLAMMATION

1. Alteration in vascular flow and caliber

2 Alteration in permeability

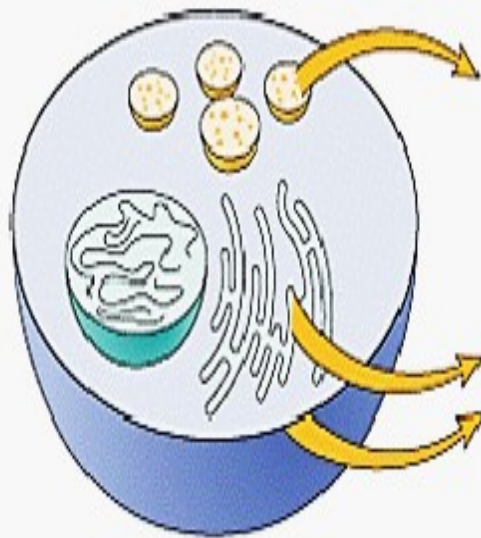
3 Emigration of leukocytes from microcirculation ,their accumulation in focus and their activation

- Histamine, bradykinin, leukotrienes
- immediate
- short lived 15 to 30 mins
- called as immediate transient response

VASCULAR CHANGES

- ❑ Vasodilation - earliest manifestation
 - -mediated by histamine and nitric oxide
- ❑ Increased permeability of microvasculature
 - Escape of protein rich fluid from blood into extra vascular space leading to edema
 - Outcome- stasis (cause neutrophils to accumulate along the vascular endothelium)

CELL-DERIVED



Preformed mediators
in secretory granules

MEDIATORS

Histamine
Serotonin

SOURCE

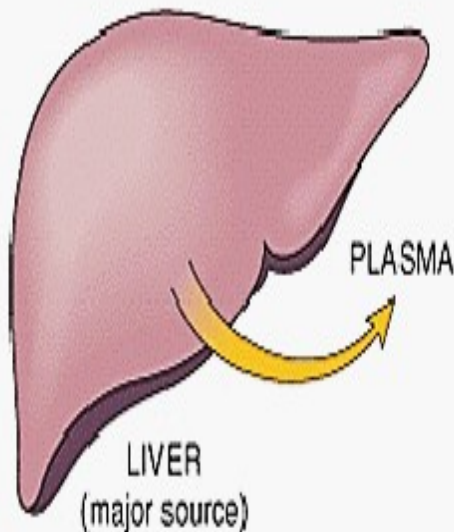
Mast cells, basophils, platelets
Platelets

Newly synthesized

Prostaglandins
Leukotrienes
Platelet-activating factor
Reactive oxygen species
Nitric oxide
Cytokines
Neuropeptides

All leukocytes, mast cells
All leukocytes, mast cells
All leukocytes, EC
All leukocytes
Macrophages, EC
Macrophages, lymphocytes, EC, mast cells
Leukocytes, nerve fibers

PLASMA PROTEIN-DERIVED



PLASMA

Complement
activation

C3a
C5a } anaphylotoxins
C3b
C5b-9 (membrane attack complex)

Factor XII (Hageman
factor) activation

Kinin system (bradykinin)
Coagulation / fibrinolysis system

CHRONIC INFLAMMATION

Chronic inflammation is a response of prolonged duration weeks or months in which inflammation , tissue injury and attempts at repair coexist in varying combination

INFLAMMATION

the NEW silent

KILLER

& how to stop it

DEAD in its tracks

MIX
NUTRITION • LIFESTYLE • MEDICINE

CAUSES OF CHRONIC INFLAMMATION

- Persistent infections by microorganism - mycobacterium ,certain viruses, fungi, parasite
- Prolonged exposure to potentially toxic agents either exogenous and endogenous
- Hypersensitivity disease
- Following acute inflammation

MORPHOLOGIC FEATURES

- Infiltration with mononuclear cells: macrophages , lymphocytes, and plasma cells
- Tissue destruction
- Attempts at healing by connective tissue replacement
- Angiogenesis
- Fibrosis

CELLS AND MEDIATORS OF CHRONIC INFLAMMATION

1) Macrophages:

- Dominant cell of chronic inflammation
- Initiates tissue repair
- Secrete inflammatory mediators (IL-1, TNF)
- Displace Ag to T lymphocytes
- Response to signal from T lymphocytes
- ❖ ACTIVATION OF MACROPHAGES: 2 MAJOR PATHWAYS
 - Classically activated
 - Alternatively activated

GRANULOMATOUS INFLAMMATION

- ❖ Granulomatous inflammation is a form of chronic inflammation characterised by collection of macrophages, often with T lymphocytes and sometimes associated with central necrosis.
- ❖ Granuloma : It is a focus of chronic inflammation consisting of microscopic aggregation of macrophages that are transformed into epithelium like cell ,surrounded by collar of mononuclear leukocytes ,principally lymphocytes and occasionally plasma cell.
- Types of granuloma:
 1. Foreign body
 2. Immune granuloma

SYSTEMIC EFFECT OF INFLAMMATION

- Fever

It is the most important manifestation of acute phase response especially when inflammation is associated with infection.

Mediated by IL-1 and TNF

- Anemia

- Leukocytosis- common in bacteria induced inflammation

- ESR elevated in all cases of chronic inflammation

CLINICAL EXAMPLES OF ACUTE AND CHRONIC INFLAMMATION

ACUTE INFLAMMATION

- 1.ACUTE SKIN INFLAMMATION
- 2.APPENDICITIS
- 3.BACTERIAL BRONCHOPNEUMONIA
- 4.CHRONIC GASTRIC ULCER

CHRONIC INFLAMMATION

1. TUBERCULOUS GRANULOMA
2. CHRONIC PANCREATITIS WITH FIBROSIS
3. PULMONARY SILICOCSIS
4. RHEUMATOID ARTHRITIS

Wound Healing

WOUND HEALING

- Wound healing is the process of repair that follows injury to the skin and other soft tissues.
- Healing is the interaction of a complex cascade of cellular events that generates resurfacing, reconstitution, and restoration of the tensile strength of injured tissue.
- Under the most ideal circumstances, healing is a systematic process, traditionally explained in terms of 3 classic phases: **inflammation, proliferation, and maturation.**

WOUND HEALING

- **The inflammatory phase:** a clot forms and cells of inflammation debride injured tissue.
- **The proliferative phase:** epithelialization, fibroplasia, and angiogenesis occur; additionally, granulation tissue forms and the wound begins to contract.
- **The maturation phase:** Collagen forms tight cross-links to other collagen and with protein molecules, increasing the tensile strength of the scar.

I. INFLAMMATORY PHASE

- **Immediate to 2-5 days**
- **B Hemostasis**
 - Vasoconstriction
 - Platelet aggregation
 - Thromboplastin makes clot
- **C Inflammation**
 - Vasodilation
 - Phagocytosis

II. PROLIFERATIVE PHASE

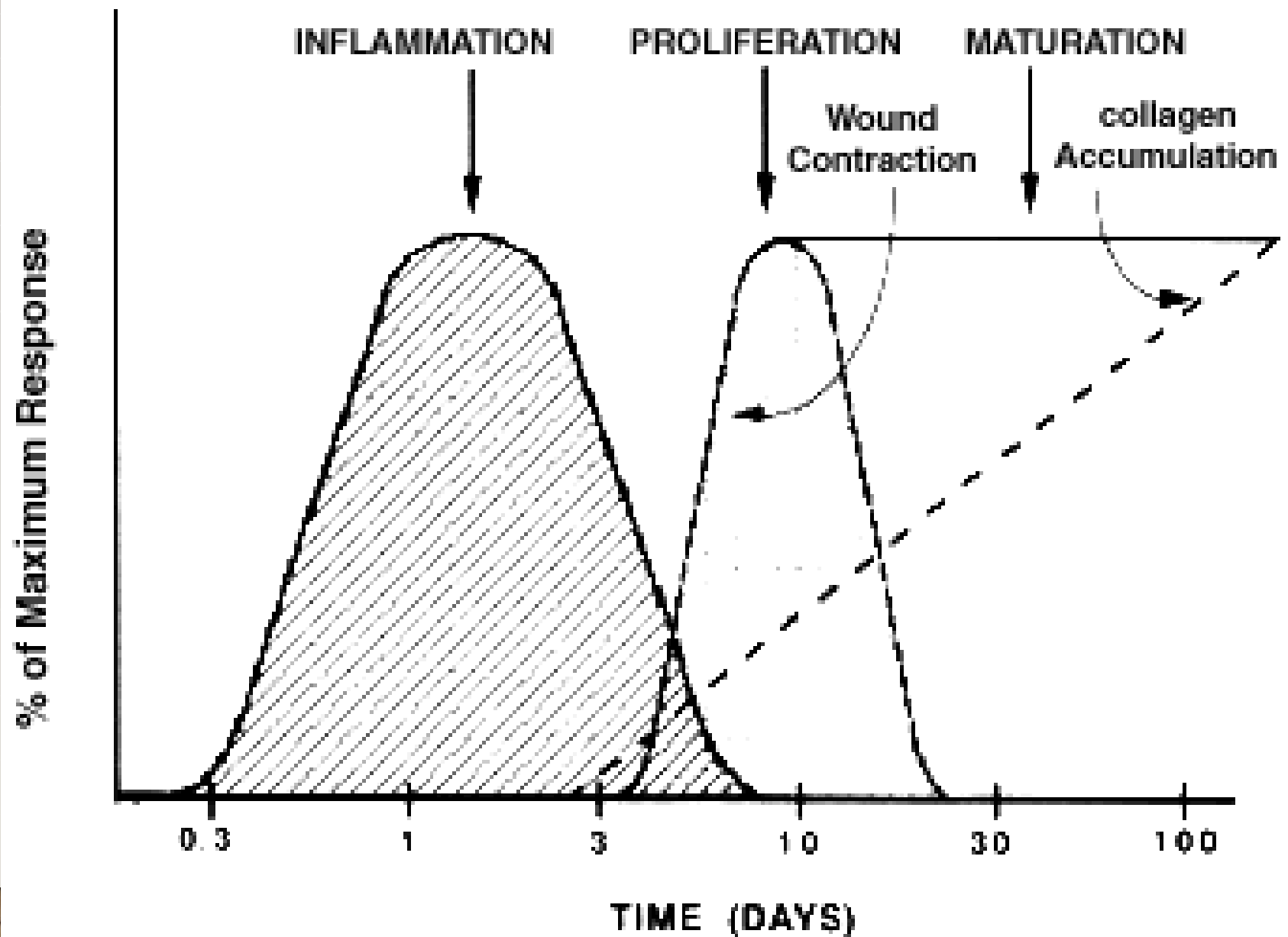
- **A) 2 days to 3 weeks**
- **B) Granulation**
 - Fibroblasts lay bed of collagen
 - Fills defect and produces new capillaries
- **C) Contraction**
 - Wound edges pull together to reduce defect
- **D) Epithelialization**
 - Crosses moist surface
 - Cell travel about 3 cm from point of origin in all directions

III. REMODELING (MATURATION) PHASE

- 3 weeks to 2 years
- B) New collagen forms which increases tensile strength to wounds. Scar tissue is only 80 percent as strong as original tissue

SCAR FORMATION

- The process of wound healing is essentially similar in all tissues and is relatively independent of the mode of injury; however, slight variation in the relative contribution of the different elements to the overall result may occur.
- The final product of the healing process is a **scar**. This relatively avascular and acellular mass of collagen serves to restore tissue continuity, strength and function.
- **Delays** in the healing process cause the prolonged presence of wounds, while
- **abnormalities** of the healing process may lead to **abnormal scar formation**.



INFLAMMATORY PHASE

- The body responds quickly to any disruption of the skin's surface.
- The early events of wound healing are characterized by a vascular and cellular response to injury.
- An incision made through a full thickness of skin causes a disruption of the microvasculature and immediate hemorrhage.
- Within seconds of the injury, blood vessels constrict to control bleeding at the site. Platelets coalesce within minutes to stop the bleeding and begin clot formation.

INFLAMMATORY PHASE

Following incision of the skin, a 5- to 10-minute period of **vasoconstriction** ensues, mediated by epinephrine, norepinephrine, prostaglandins, serotonin, and thromboxane.

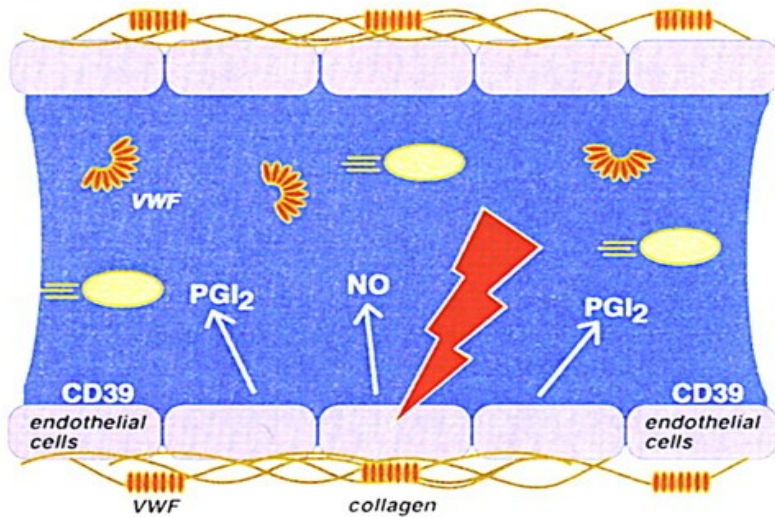
Vasoconstriction causes temporary blanching of the wound and functions to reduce hemorrhage immediately following tissue injury, aid in platelet aggregation, and keep healing factors within the wound.

INFLAMMATORY PHASE

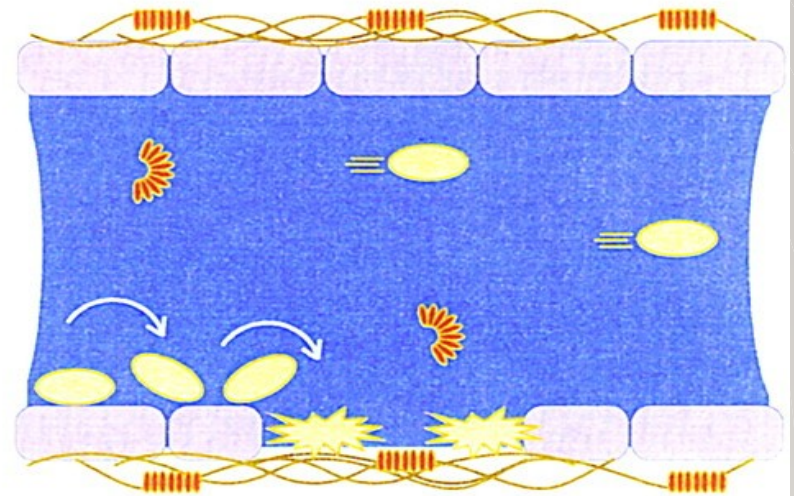
- Endothelial cells **retract** to expose the subendothelial collagen surfaces; **platelets attach** to these surfaces.
- **Adherence** to exposed collagen surfaces and to other platelets occurs through **adhesive glycoproteins**: fibrinogen, fibronectin, thrombospondin, and von Willebrand factor.

Stages in platelet plug formation

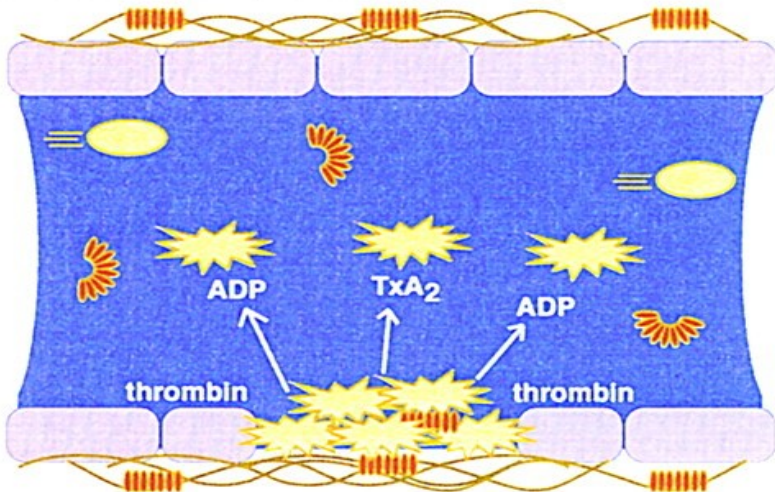
A. Injury



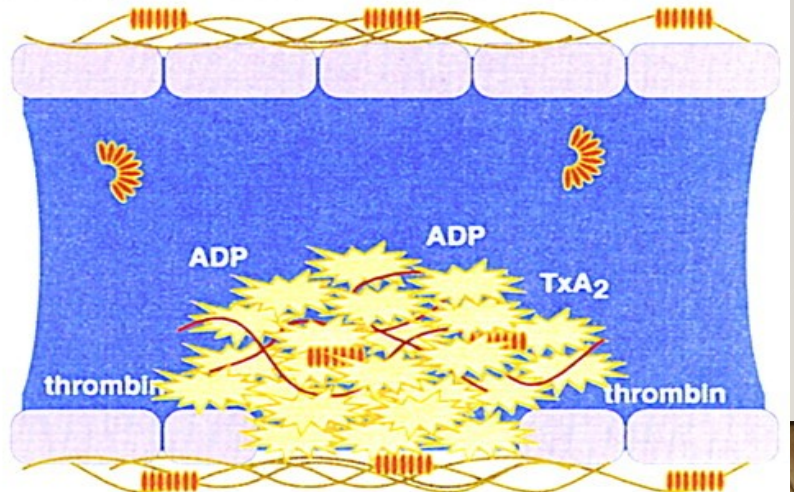
B. Initiation



C. Extension (recruitment)



D. Perpetuation (stabilization)



INFLAMMATORY PHASE

- In addition to activation of fibrin, thrombin facilitates migration of inflammatory cells to the site of injury by **increasing vascular permeability**. By this mechanism, factors and cells necessary to healing flow from the intravascular space and into the extravascular space.

PROLIFERATION PHASE

- On the surface of the wound, **epidermal cells** burst into mitotic activity within **24 to 72 hours**. These cells begin their migration across the surface of the wound.
- **Fibroblasts** proliferate in the deeper parts of the wound. These fibroblasts begin to synthesize small amounts of collagen which acts as a scaffold for migration and further fibroblast proliferation.

PROLIFERATION PHASE

- **Granulation tissue**, which consists of capillary loops supported in this developing collagen matrix, also appears in the deeper layers of the wound. The proliferation phase lasts from **24 to 72 hours** and leads to the fibroblastic phase of wound healing.

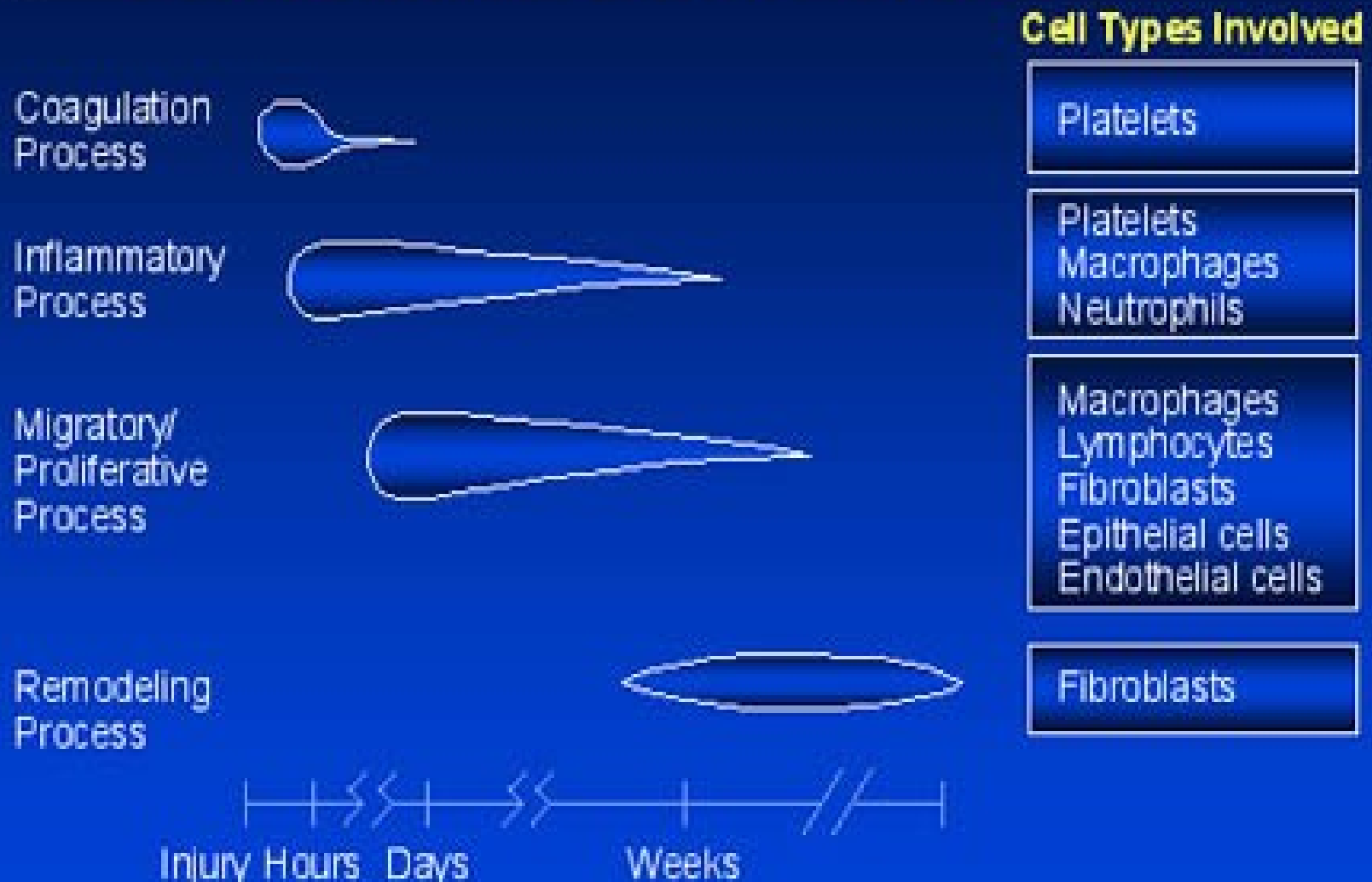
PROLIFERATION PHASE

- ~~Four to five days~~ after the injury occurs, fibroblasts begin producing large amounts of collagen and proteoglycans.
- Collagen fibers are laid down randomly and are cross-linked into large, closely packed bundles.

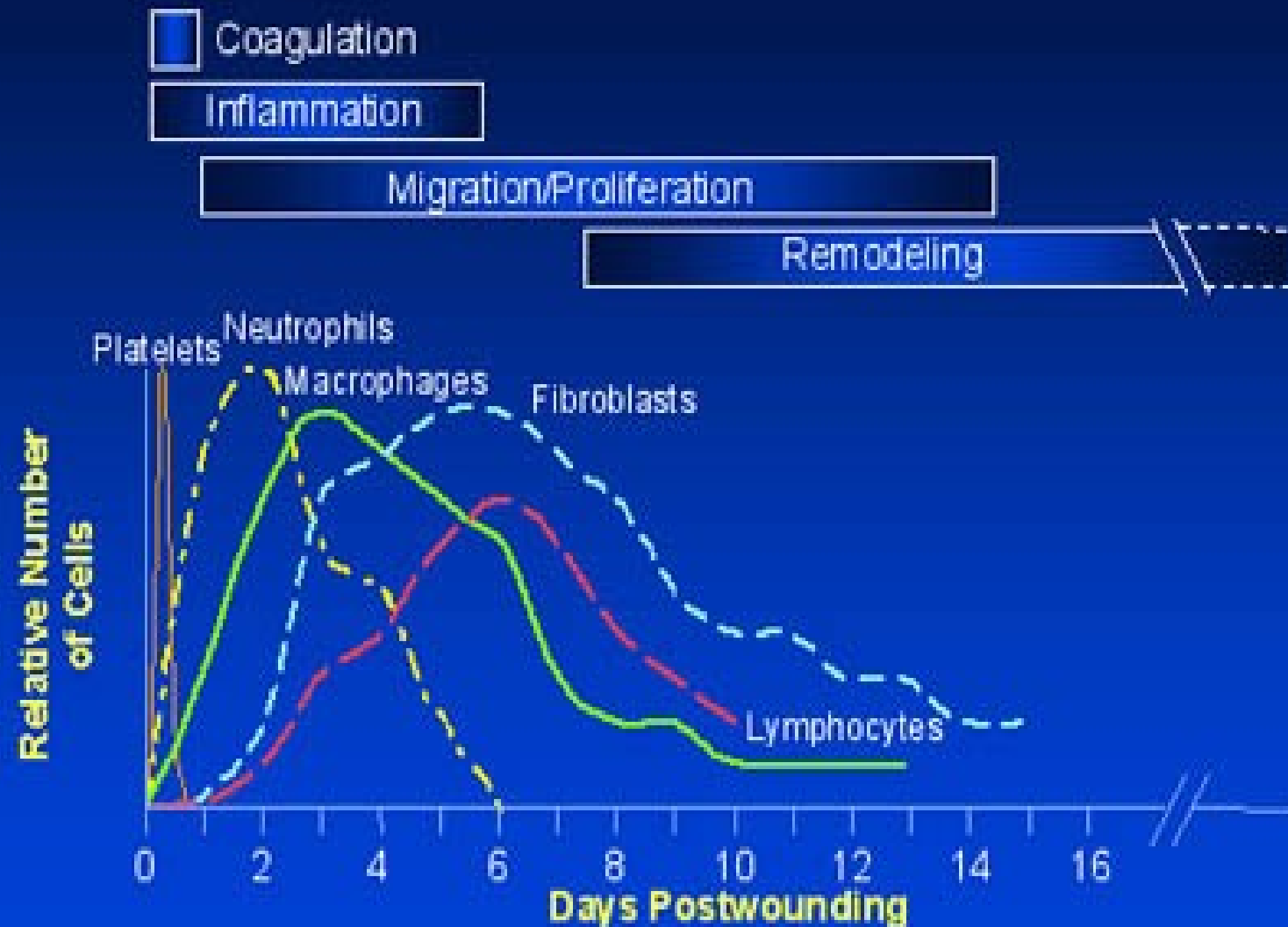
MATURATION PHASE

- During the maturation phase, **fibroblasts leave the wound and collagen is remodeled** into a more organized matrix.
- **Tensile strength increases** for up to one year following the injury. While healed wounds never regain the full strength of uninjured skin, they can regain up to 70 to 80% of its original strength.

COMPONENTS OF WOUND HEALING

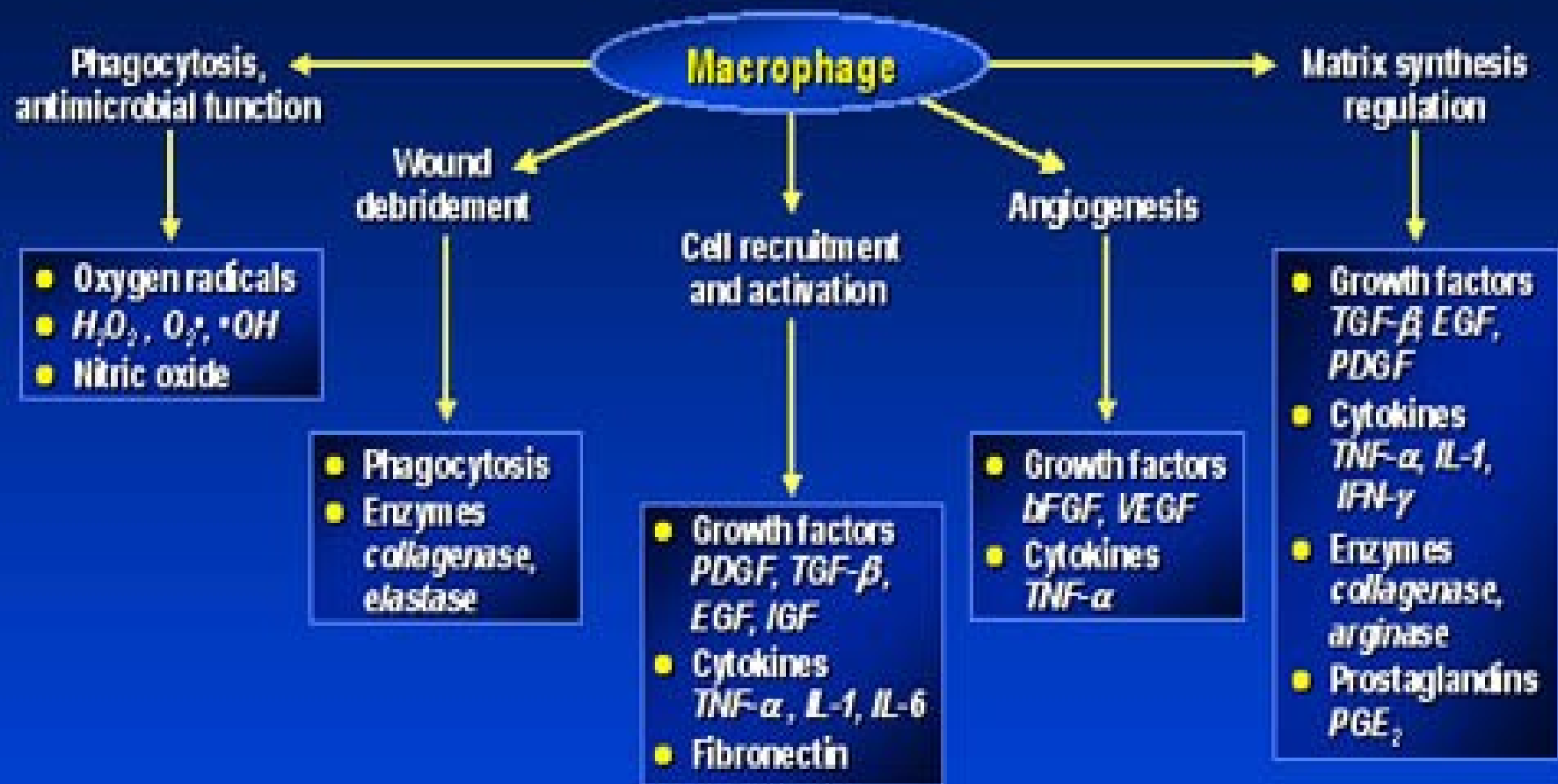


CELL RECRUITMENT IN THE WOUND



Adapted with permission from Witte MB and Barbul A. *Surg Clin North Am.* 1997;77:512.

ROLE OF MACROPHAGES IN WOUND HEALING



MIGRATION/PROLIFERATION

Angiogenesis

- Formation of vessels
 - Begin as endothelial cell buds
 - Progress toward wound space, following oxygen gradient
 - Immature vessels differentiate into capillaries, arterioles, and venules
 - Macrophages and keratinocytes provide angiogenic stimuli

HEALING RETARDED BY SEVERAL FACTORS

- Ischemia
- Dry wound environment
- Infection
- Foreign bodies
- Anti-inflammatory therapy
- Nutritional deficiency

Haimowitz JE, Margolis DJ. In: *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Health Management Publications Inc; 1997:49-56.

Hunt TK, Zabel DD. In: *Textbook of Critical Care*. 3rd ed. WB Saunders Co; 1995:1475-1486.

HEALING PROCESS: ACUTE WOUNDS

- Sequence completed in continuous and expected time frame
- Usually achieved with few or no complications
- Overreaction in acute wound healing
 - Keloids
 - Hypertrophic scars

LOCAL FACTORS AFFECTING WOUND HEALING

- Mechanical injury
- Infection
- Edema
- Ischemia/necrotic tissue
- Topical agents
- Ionizing radiation
- Low oxygen tension
- Foreign bodies

REGIONAL FACTORS AFFECTING WOUND HEALING

- Arterial insufficiency
- Venous insufficiency
- Neuropathy

FUTURE OF WOUND HEALING

- Continued research
 - Elucidation of signals/growth factors involved in:
 - epithelization
 - wound contraction and scarring
 - angiogenesis
- Tissue engineering
- Gene therapy



The
End